ORIGINAL ARTICLE

Four gland parathyroidectomy without reimplantation in patients with chronic renal failure

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Background: The optimal surgical management of patients in end stage chronic renal failure with secondary hyperparathyroidism is controversial. One approach advocated is four gland parathyroidectomy without reimplantation. The aim of this study was to review the medium term results of this procedure.

Methods: Fifty four consecutive patients with end stage chronic renal failure and secondary hyperparathyroidism who had a four gland parathyroidectomy without reimplantation were studied. The procedure was performed by a single surgeon with a median (range) follow up of 29 (0–70) months.

Results: Most patients (76%) developed postoperative hypocalcaemia but this was easily treated and doses of long term drugs necessary to prevent this were low. Pre-operative bone symptoms, hypercalcaemia, hyperphosphataemia, and an increased alkaline phosphatase were improved or resolved in most patients. Thirteen (24%) patients had an undetectable postoperative parathyroid hormone (PTH), (6 of 12 (50%) with a functioning renal transplant and 7 of 42 (17%) who required dialysis, p = 0.02). Median (range) postoperative PTH values in these groups were 0.1 (0.1–31) compared with 1.0 (0.1–24) pmol/l (p = 0.085) respectively. The remaining 41 of 54 (76%) patients had residual PTH secretion and postoperative hyperparathyroidism was identified in eight (15%) patients with only two requiring neck re-exploration.

Conclusion: Four gland parathyroidectomy without reimplantation produced good medium term biochemical and clinical results. Most patients had minor residual PTH secretion that may contribute to this and mitigate concerns regarding adynamic bone disease. Endogenous PTH secretion is only completely lost in a few patients but occurs more often in those with a functioning renal transplant. Bone densitometry is required to investigate the long term impact of this procedure.

Secondary hyperparathyroidism is a common complication of end stage renal failure (ESRF) and despite improved medical management, 0.67%–1.4% of dialysis dependent patients require parathyroidectomy annually.[1] The pathophysiological stimulus causing hyperparathyroidism persists throughout the lifetime of these patients but is temporarily abated by a functioning renal transplant (mean cadaveric half life 13.7 years).[2] Both subtotal parathyroidectomy and total parathyroidectomy with reimplantation leave a significant amount of parathyroid tissue in situ that may in turn become hyperplastic producing recurrent hyperparathyroidism.[3 4] Re-explorations of the neck and surgery on appendicular intramuscular parathyroid tissue are complicated and can cause significant morbidity.[5–7] In view of this total parathyroidectomy without reimplantation has been advocated.[8]

Most people have four parathyroid glands with only 2%–6% having five or more.[9] Therefore most patients who have a four gland parathyroidectomy have had a total parathyroidectomy. The important criticism of this approach is that a complete absence of parathyroid hormone (PTH) may cause severe postoperative hypocalcaemia, a long term requirement for excessive treatment to correct this, and in addition may prevent the normal physiological mineralisation and turnover of bone resulting in adynamic bone disease.[10–12] The aim of this study was to review the clinical results from this procedure in the medium term to assess the efficacy of this approach.

METHODS

Study population

Fifty four consecutive ESRF patients who underwent four gland parathyroidectomy without reimplantation between 1994 and 1999 were studied. The 41 dialysis dependent patients and five patients who underwent this procedure before receiving a successful renal transplant had secondary hyperparathyroidism. The seven patients who had hyperparathyroidism that persisted after successful renal transplantation presumably had tertiary hyperparathyroidism at the time of parathyroidectomy. Table 1 shows patient characteristics, current renal replacement strategy, preoperative biochemistry, and indications for surgical intervention. All patients had a raised pre-operative serum PTH and many had more than one clinical indication for surgery. The most common were bone pain, significant biochemical/radiological evidence of bone disease, and hypercalcaemia. Median (range) follow up was 29 (0–70) months.

Operative technique

Preoperative imaging of the parathyroid glands was not routinely used. Patients underwent dialysis as required and received 10 μg of 1-α calcidol the day before surgery in an effort to prevent severe postoperative hypocalcaemia. All operations were performed by a single consultant surgeon with a standard collar incision. The strap muscles were retracted laterally and four parathyroid glands identified and excised. Thymectomy was not performed routinely if four parathyroid glands had been confidently removed. If this was not the case then a thymectomy was undertaken as the thymus is a not infrequent site of aberrant parathyroid glands. All resected tissue was histologically verified initially by intraoperative frozen section and subsequently

Abbreviations: ESRF, end stage renal failure; PTH, parathyroid hormone

Table 1 Patient characteristics, symptoms, and preoperative biochemistry

Parameter	
Age (y)	51 (19–72)
Sex (M:F)	29:25
Pre-dialysis	1 (2)
Haemodialysis	21 (39)
Peritoneal dialysis	20 (37)
Renal transplant	12 (22) 5 preTx, 7 postTx
Duration of dialysis (months)	37 (1–360)
Symptoms	
Bone pain	28 (52)
Persistent hypercalcaemia	27 (50)
Pathological fractures	3 (6)
Soft tissue calcification	5 (9)
Pruritis	13 (24)
Epo resistant anaemia	1 (2)
Preoperative biochemistry (normal range)	
PTH (1.3–7.6 pmol/l)	89 (24–270)
Ca^{2+} (2.2–2.6 mmol/l)	2.62 (2.15–3.40)
PO_4 (0.8–1.4 mmol/l)	2.01 (0.34–3.46)
Alkaline phosphatase (40–130 mmol/l)	144 (56–911)

Median values (range in parentheses) and raw data (percentage of each group in parentheses) are presented. PreTx, parathyroidectomy before renal transplant; PostTx, parathyroidectomy after renal transplant.

using conventional histological examination. At the end of the procedure a central venous cannula was placed under direct vision into the right internal jugular vein to permit administration of calcium gluconate if required postoperatively. Before wound closure a cytostatic solution of chlorhexidine acetate 0.015% and cetrimide 0.15% (Baxters Health Care Ltd, UK) was applied to the operative field.

Postoperative care

The corrected serum calcium concentration was followed up every four hours for the first two days postoperatively and if this fell below 2.0 mmol/l then 10% calcium gluconate was givent at a rate dictated by the level, as described above. Patients were supplemented orally with 1-α calcidol/ calcichew tablets and the central line removed when no longer required. Serum calcium concentrations were assessed daily for a 7–14 day period until stable and thereafter at regular clinic follow up. The dose of 1-α calcidol and calcichew tablets was adjusted to maintain the corrected serum calcium within the normal range (2.2–2.6 mmol/l). The presence of bony symptoms at the most recent clinic appointment was recorded using a verbal scale consisting of four options (resolved, improved, unchanged, or unknown). Routine biochemistry was assessed at this time using standard auto-analytical techniques. Between 1994 and 1998 intact PTH 1–84 had a normal reference range of 0.9–5.4 pmol/l (Immuno-radiometric assay, Immuno-diagnostic systems, Tyne and Wear, UK). This was changed to the Immulite 2000 immunometric assay in 1998 with a change in the normal reference range to 1.3–7.6 pmol/l. PTH is considered absent if there is less than 0.1 pmol/l detected using this assay.

Data analysis

Data were not normally distributed and results are expressed as raw numbers (%) or median values (range). Paired and unpaired continuous variables were analysed using Wilcoxon signed rank or Mann-Whitney U tests respectively. Categorical data were compared using Fisher's exact test. A p value <0.05 was considered to be significant and $0.05<p<0.10$ considered to have marginal significance.

RESULTS

Four parathyroid glands were excised in all cases. On one occasion identification of the fourth gland proved difficult despite an extensive neck dissection. In this case a thymectomy was performed and it was identified in the thymus on pathological examination. Histopathological assessment confirmed that most procedures removed four hyperplastic glands (n = 207). Eight parathyroid adenomas and one histologically normal gland were also identified.

Postoperative hypocalcaemia and requirement for long term supplements

In the early postoperative period, a median of 2 (range 1–30) days after surgery, 41(76%) patients developed hypocalcaemia with the median lowest corrected serum calcium of 2.04 mmol/l and a range from 0.96–2.66 mmol/l. Twenty five (46%) patients required a 10% calcium gluconate infusion before stabilisation of serum calcium with oral medication. Patients were discharged with a median (range) daily dose of 7 (0.25–20) µg 1-α calcidol, which was reduced over follow up to current doses of 0.175 (0–10) µg. Oral calcium supplementation displayed a similar pattern with median (range) daily doses at discharge of 6 (0–16) Calcichew (Shire) tablets/day that had reduced to 0 (0–9) tablets/day at most recent clinic follow up.

Clinical and biochemical results

There were no re-explorations required for bleeding. One patient complained of a hoarse voice that resolved without treatment. Two patients died in the early postoperative period secondary to a chest infection and severe ischaemic heart disease. The overall clinical and biochemical responses to total parathyroidectomy were good. Preoperative bone symptoms were abolished or improved in 23 of 28 (82%) patients, no pathological fractures occurred, and the case of Epo resistant anaemia resolved. Preoperative hypercalcaemia, hyperphosphataemia, and an increased alkaline phosphatase were normalised or improved in 25 of 27 (93%), 31 of 45 (69%), and 29 of 33 (88%) respectively. Corrected serum calcium, phosphate, and alkaline phosphatase values were significantly reduced compared with preoperative values (table 1) after surgery (median (range) $cCa^{2+} = 2.45$ (1.75–3.26) mmol/l, $p<0.01$; $PO_4 = 1.62$ (0.46–3.47) mmol/l, $p = 0.04$; alkaline phosphatas = 82 (41–491) mmol/l, $p<0.01$).

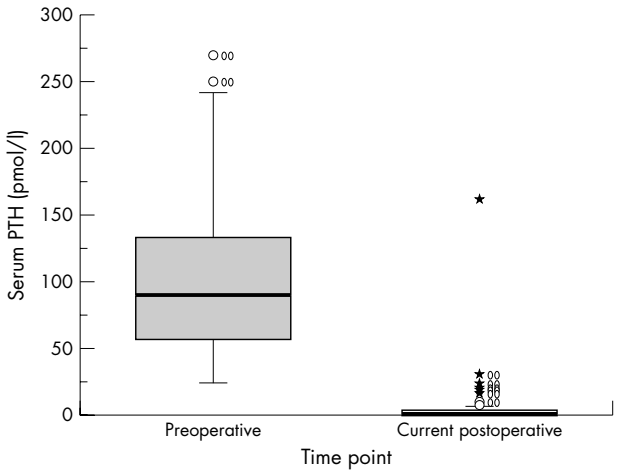

Figure 1 Change in serum PTH after total parathyroidectomy. Median, interquartile range, outliers, and extreme values are shown by horizontal bar, shaded box, error bars, and individual markers respectively.

Postoperative PTH and hyperparathyroidism

Figure 1 shows the median latest postoperative PTH values that, as expected, had declined significantly after surgery. Serum PTH was undetectable (<0.1 pmol/l) in 13 (24%) patients. A further four patients who had an undetectable PTH initially had developed a detectable PTH (0.4, 0.6, 1.1, and 1.6 pmol/l respectively) over follow up. Thirty three (61%) patients had biochemically detectable serum PTH and although six of these had increased over follow up, all remained in the physiological range (1.3–7.6 pmol/l).

Eight patientss (15%) developed postoperative hyperparathyroidism, defined by a serum PTH higher than 7.6 pmol/l. One had persistent hyperparathyroidism (shown by supraphysiological PTH values in the immediate postoperative period) and seven developed recurrent hyperparathyroidism (identified by a PTH that increased above the normal range over follow up). In this second group the median (range) PTH at latest follow up was 19 (9.2–31) pmol/l. Two (4%) neck re-explorations were performed. The patient with persistent disease had ongoing bone pain with a PTH of 120 pmol/l. A parathyroid adenoma was excised from an area adjacent to the left lower pole of the thyroid producing a fall in PTH (latest 24 pmol/l) and resolution of pain. A second patient developed hypercalcaemia and a PTH of 102 pmol/l 24 months after four gland parathyroidectomy. At the initial operation one parathyroid gland was split perioperatively possibly accounting for these findings. At re-exploration a nodular hyperplastic gland was removed from an area adjacent to the right upper pole of the thyroid and currently the postoperative PTH is undetectable (<0.1 pmol/l).

The impact of renal transplantation on postoperative PTH

Median (range) preoperative PTH (71.5 (26.9–190) compared with 93 (24.1–170), p = 0.32) and length of follow up (23 (5–70) compared with 34 (6–70) months, p = 0.43) was similar for those who had a functioning renal transplant and those requiring regular renal dialysis. Figure 2 compares the latest postoperative PTH of these groups. Although only of marginal significance (p = 0.085), it is worth noting that patients with a functional renal transplant had lower postoperative PTH values than their counterparts requiring dialysis. Furthermore, a greater proportion of those with a renal transplant had an undetectable postoperative PTH (6 of 12 (50%) compared with 7 of 42 (17%), p = 0.02). The timing of parathyroidectomy in relation to renal transplantation had no significant impact on postoperative PTH.

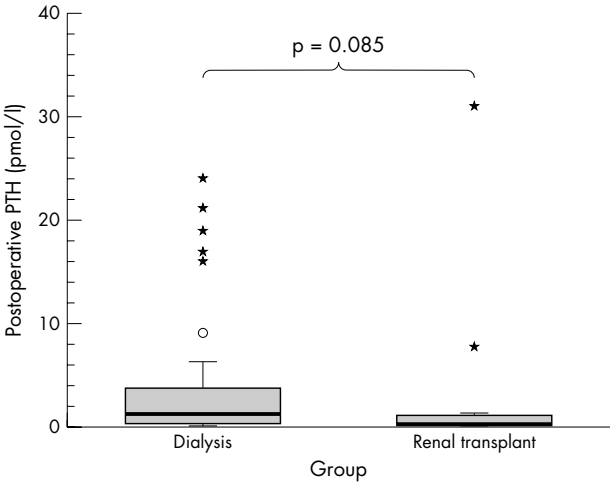

Figure 2 Comparison of postoperative PTH in dialysis dependent patients and renal transplant recipients. Median, interquartile range, outliers, and extreme values are shown by horizontal bar, shaded box, error bars, and individual markers respectively. p = 0.085 compared with dialysis group, Mann-U-Whitney test.

DISCUSSION

Large series of both subtotal and total parathyroidectomy with re-implantation have been published in patients with ESRF[3 13] but there has been less interest in four gland parathyroidectomy without reimplantation. This study suggests that the medium term results from this approach compare favourably with other strategies.

Early postoperative hypocalcaemia was common but administration of 10% calcium gluconate via a central line placed perioperatively facilitated the management of patients before stabilisation with oral medication. In the longer term, doses of 1-α calcidol and oral calcium supplements were low. Furthermore, preoperative bone symptoms, serum alkaline phosphatase, and hypercalcaemia were improved or normalised in most patients. Minor residual PTH secretion was not uncommon, but there was a low prevalence of postoperative hyperparathyroidism (15%). The definition of recurrent hyperparathyroidism in the literature is inconsistent and varied with length of follow up but these results are similar to other smaller series of four gland parathyroidectomy without reimplantation (13%–43%).[14–16] Recurrent hyperparathyroidism may be more common after both subtotal and total parathyroidectomy with reimplantation (0%–80%).[16–21] However, only one small retrospective study has attempted to compare all three approaches. Re-exploration of the neck for recurrent disease did not occur after four gland parathyroidectomy without implantation but was necessary on two occasions after the other strategies.[22]

The proportion (24%) of patients with no detectable serum PTH postoperatively is similar to other smaller series of total parathyroidectomy without implantation (10%–22%).[14 15 22 23] During the embryological development of the parathyroid glands it has been suggested that microscopic islands "rests" of parathyroid tissue can be deposited anywhere along the descent of the glands from the third and fourth branchial pouches.

Hyperplasia of these microscopic "rests" attributable to the persistent stimulus created by ongoing ESRF may occur resulting in detectable PTH in the longer term despite four gland parathyroidectomy.[15 25] The presence of detectable but low postoperative PTH in many of the patients studied may reflect this. Furthermore, PTH increased over follow up in one third of these, four of whom originally had an undetectable PTH. Such findings may well mitigate concerns regarding adynamic bone disease because of a lack of postoperative PTH. There is little work in this area but one small study (n = 13) noted increased lumbar vertebra and femoral neck bone density after total parathyroidectomy without reimplantation (3.8 years mean follow up).[24]

Concurrent thymectomy was not routinely performed if four parathyroid glands were removed in the current series. If less than four were identified then thymectomy was performed. This was based on the rationale that supernumerary glands are uncommon (only 2%–6% of patients have five or more glands[9]) and not necessarily located in the thymus. This potentially controversial approach proved reasonable as only one patient had evidence of persistent hyperparathyroidism in the immediate postoperative period and on re-exploration a fifth gland was identified and removed without thymectomy. Furthermore, it is quite possible that some of the parathyroid "rests" responsible for postoperative PTH secretion lie within the thymus. Although bone densitometry evidence is limited, these may be important in reducing the risks of adynamic bone disease, providing a further argument against thymectomy.

The second patient that required re-exploration developed recurrent hyperparathyroidism secondary to an area of nodular hyperplasia adjacent to the right upper lobe of the thyroid and this was also excised without thymectomy. It may have developed because of seeding into the wound after splitting of a gland in the perioperative period. This is an important technical point for the surgeon to observe as such seeding is a preventable cause of recurrent disease. Furthermore, because seeded cells do not have an intact gland capsule the appearances can potentially mimic neoplasia at reoperation. The use of cytostatic fluid over the operative field at the original procedure in an attempt to prevent seeding is anecdotal and in this instance proved ineffective.

The stimulus to secrete parathyroid hormone and develop parathyroid hyperplasia is considerably reduced after successful transplantation when renal function is improved. This may explain the trend towards a lower postoperative PTH and the significant number (6 of 12, 50%) of renal transplant recipients who currently have undetectable PTH values. Such patients may be aparathyroid for a decade or longer before recurrent renal impairment causes significant hyperplasia of remnant tissue. This may place them at greater risk of adynamic bone disease compared with the dialysis dependent population.

Four gland parathyroidectomy without implantation represents a pragmatic solution for ESRF patients with secondary hyperparathyroidism. However, it is possible that the optimal surgical strategy may be different in patients who plan to remain on renal dialysis indefinitely than in those who are awaiting or possess a functioning renal transplant. Theoretically four gland parathyroidectomy without reimplantation may suit the former more than the latter in view of the increased frequency of very low or undetectable PTH in renal transplant recipients. A prospective randomised trial comparing it with both subtotal and total parathyroidectomy with reimplantation would clearly help to resolve this. Ideally this would include bone densitometry to clarify the importance of adynamic bone disease.

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REFERENCES

1 **Cohen EP**, Moulder JE. Parathyroidectomy in chronic renal failure: Has medical care reduced the need for surgery? *Nephron* 2001;**89**:271–4.
2 **Hariharan S**, Johnson CP, Bresnahan BA, *et al.* Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med* 2000;**342**:605–12.
3 **O'Leary DP**, White HJO. Parathyroidectomy for hyperparathyroidism associated with renal disease. *Ann R Coll Surg Engl* 1995;**77**:97–101.
4 **Gagne ER**, Urena P, Leite-Silva S, *et al.* Short and long term efficacy of total parathyroidectomy with immediate autografting compared with subtotal parathyroidectomy in haemodialysis patients. *J Am Soc Nephrol* 1992;**3**:1008–17.
5 **Patow CA**, Norton JG, Brennan MF. Vocal cord paralysis and reoperative parathyroidectomy. *Ann Surg* 1986;**203**:282–6.
6 **Freid U**, Klempa I, Schneider M, *et al.* Tumour like growth of parathyroid autografts in uraemic patients. *Proc Eur Dialy Transplant Assoc* 1981;**18**:548–55.
7 **Ellis SH**. Fate of long term parathyroid autografts in patients with chronic renal failure treated by parathyroidectomy: a histopathological study of autografts, parathyroid glands and bone. *Histopathology* 1988;**13**:289–309.
8 **Ogg CS**. Total parathyroidectomy in treatment of secondary (renal) hyperparathyroidism. *BMJ* 1967;ii:331–4.
9 **Wang CA**. The anatomic basis of parathyroid surgery. *Ann Surg* 1976;**183**:271.
10 **Felsenfeld AJ**, Harrelson JM, Gutman RA, *et al.* Osteomalacia after parathyroidectomy in patients with uraemia. *Ann Intern Med* 1992;**96**:34–9.
11 **Malluche HH**, Akmal M, Goldstein DA, *et al.* The role of the lack of parathyroid hormone in the pathogenesis of uraemic low turnover osteomalacia. *Kid Int* 1982;**21**:137.
12 **Hercz G**, Pei Y, Greenwood C, *et al.* Aplastic osteodystrophy without aluminium. The role of suppressed parathyroid function. *Kid Int* 1993;**44**:860–6.
13 **Henry JFR**, Denizot A, Audiffret J, *et al.* Results of reoperations for persistent or recurrent hyperparathyroidism in haemodialysis patients. *World J Surg* 1990;**14**:303–7.
14 **Ljutic D**, Cameron JS, Ogg CS, *et al.* Long term follow-up after total parathyroidectomy without parathyroid reimplantation in chronic renal failure. *Q J Med* 1994;**87**:685–92.
15 **Farrington K**, Varghese Z, Chan MK, *et al.* How complete is total parthyroidectomy in uraemia? *BMJ* 1987;**294**:743.
16 **Stracke S**, Jehle PM, Sturm D, *et al.* Clinical course after total parathyroidectomy without autotransplantation in patients with end stage renal failure. *Am J Kid Dis* 1999;**33**:304–11.
17 **Higgins RM**, Richardson AJ, Ratcliffe PJ, *et al.* Total parathyroidectomy alone or with autograft for renal hyperparathyroidism? *Q J Med* 1991;**79**:323–32.
18 **Koosman M**, Hughes K, Dickerman R, *et al.* Parathyroidectomy in chronic renal failure. *Am J Surg* 1994;**168**:631–5.
19 **Rothmund M**, Wagner PK, Schark C. Subtotal parathyroidectomy versus total parathyroidectomy and autotransplantation in secondary hyperparathyroidism. A randomised trial. *World J Surg* 1991;**15**:745–50.
20 **Z**, Magen H, Kraus L, Bernheim J. Total parathyroidectomy with autotransplantation in haemodialysis patients with secondary hyperparathyroidism. Should it be abandoned? *Neph Dial Transplant* 1987;**2**:341–6.
21 **Hampl H**, Steinmuller T, Stabell U, *et al.* Recurrent hyperparathyroidism after total parathyroidectomy and autotransplantation in patients on long term haemodialysis. *Miner Electrolyte Metab* 1991;**17**:256–6.
22 **Nicholson ML**, Veitch PS, Feehally J. Parathyroidectomy in chronic renal failure. A comparison of 3 operative strategies. *J R Coll Edinb* 1996;**41**:382–7.
23 **Kaye M**, D'Amour P, Henderson J. Elective total parathyroidectomy without autotransplantation in end stage renal disease. *Kid Int* 1989;**35**:1390–9.
24 **Kaye M**, Rosenthall L, Hill RO, *et al.* Long term outcome following total parathyroidectomy in patients with end stage renal disease. *Clin Nephol* 1993;**39**:192–7.
25 **Reddick RL**, Costa JC, Marx SJ. Parathyroid hyperplasia and parathyromatosis. *Lancet* 1977;ii:509.